NTP
National Toxicology Program

Non-Neoplastic Renal Lesions of F344 Rats Exposed to β-Myrcene

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NTP Board of Scientific Counselors
Technical Reports Review Subcommittee Meeting

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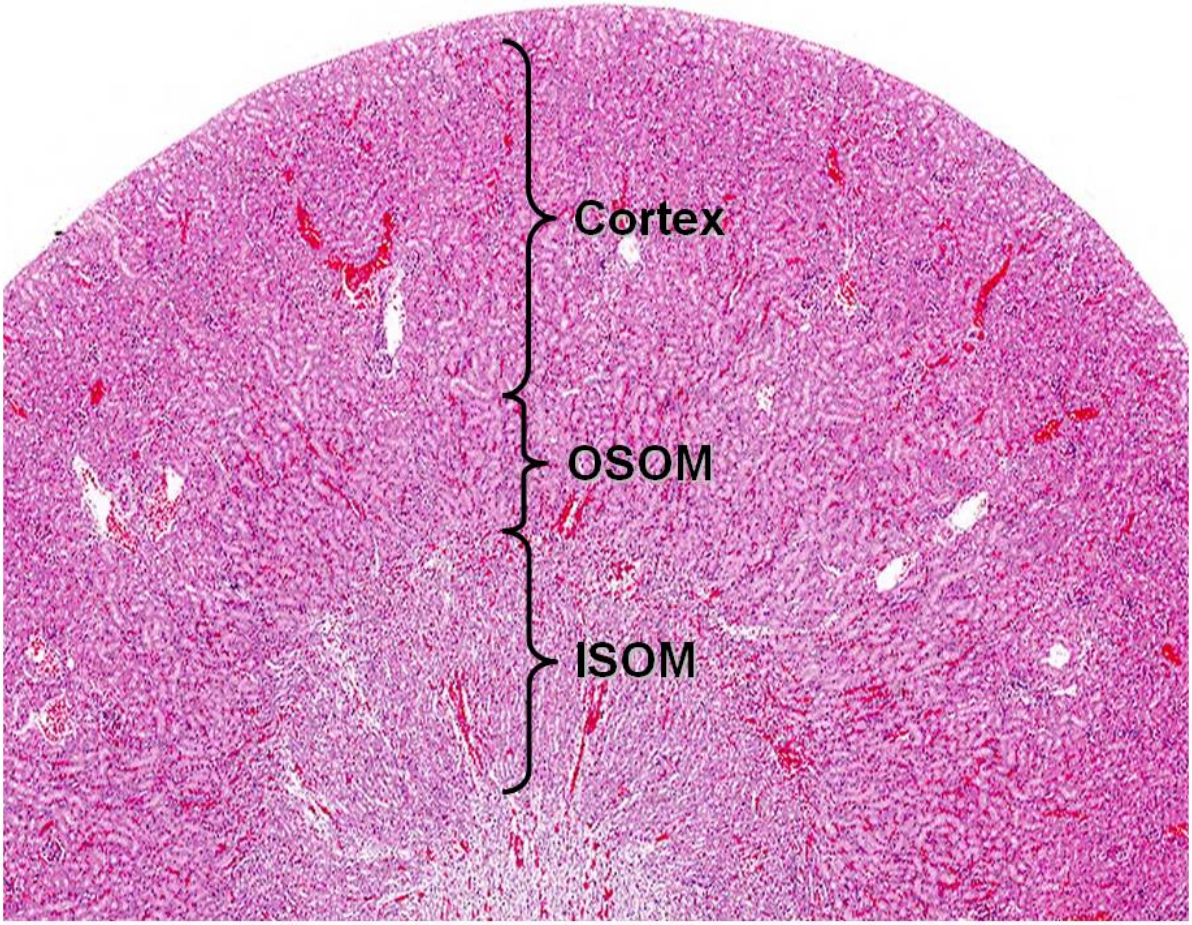
Non-neoplastic renal lesions of F344 rats exposed to β-myrcene

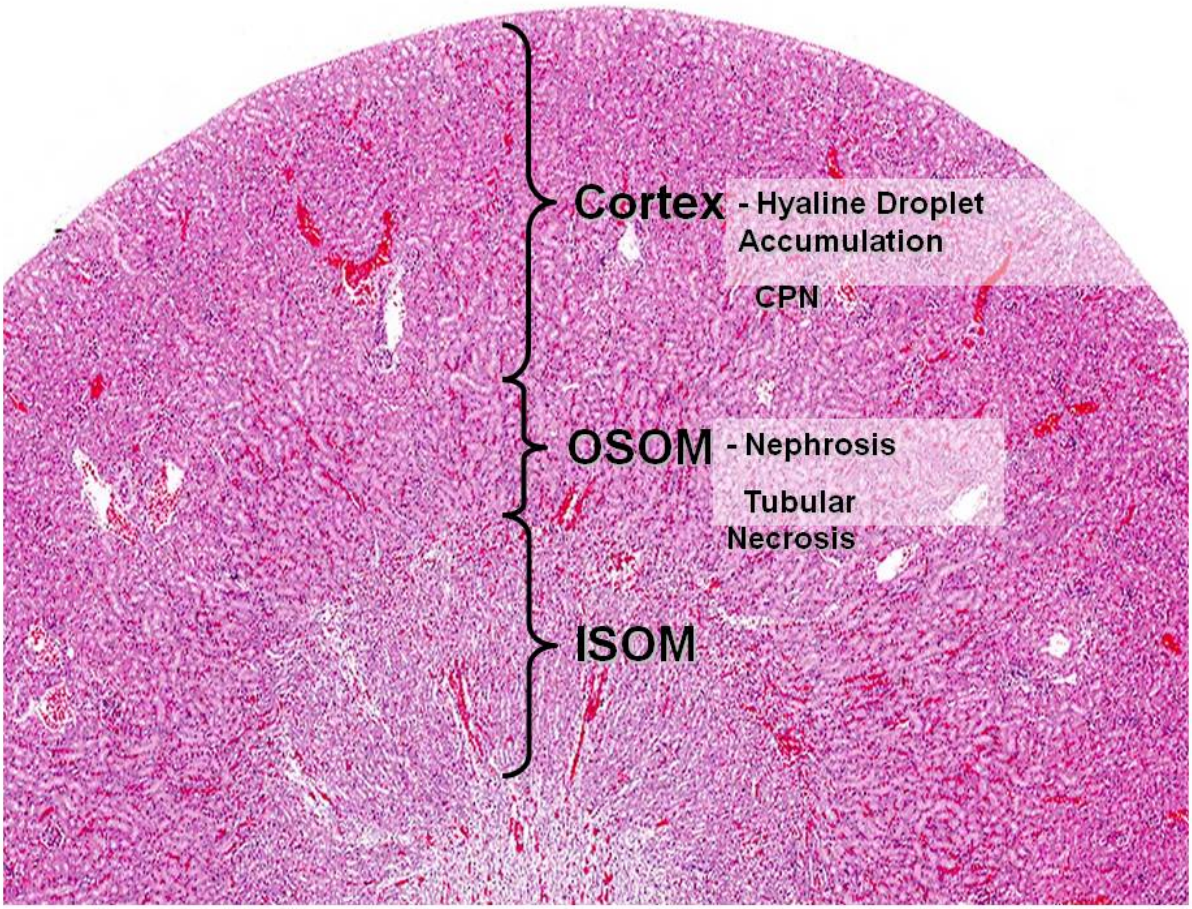
90-Day Study

- Tubular Necrosis
- Nephrosis
- Chronic Progressive Nephropathy (CPN)
- Hyaline Droplet Accumulation (HDA)

2-Year Study

- Nephrosis
- Chronic Progressive Nephropathy (CPN)
- Linear Papillary Mineralization

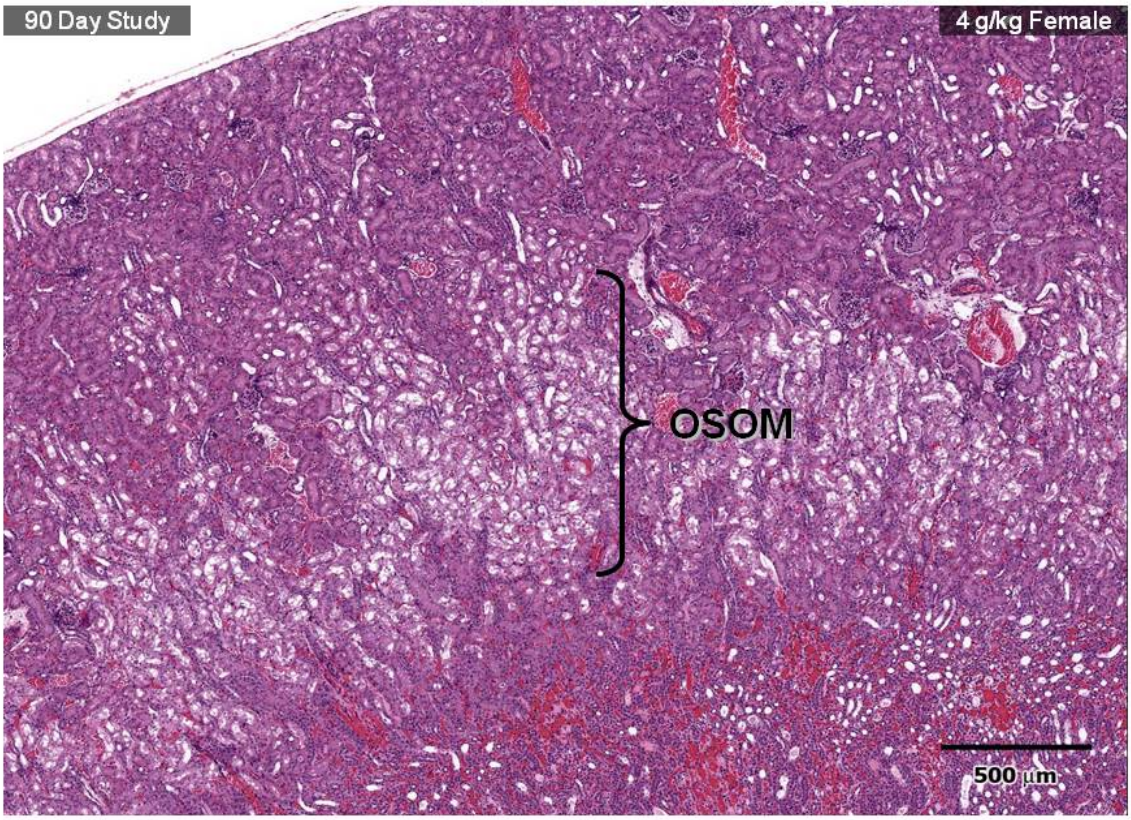

Cortex
OSOM
ISOM


Cortex
- Hyaline Droplet Accumulation
CPN
OSOM
- Nephrosis
Tubular Necrosis
ISOM

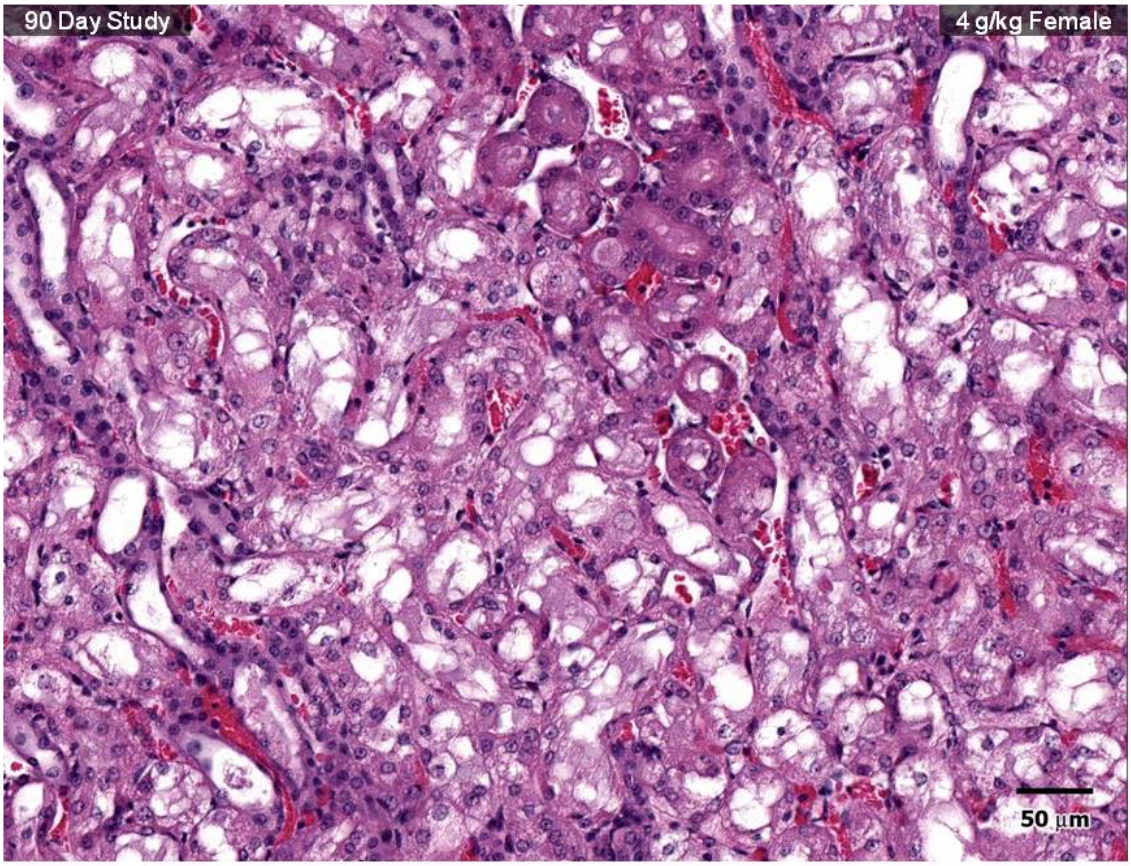
Tubular Necrosis

- 90-Day
- Males and Females
- OSOM
- Minimal to moderate severity that increased with dose

OSOM: Tubular Necrosis



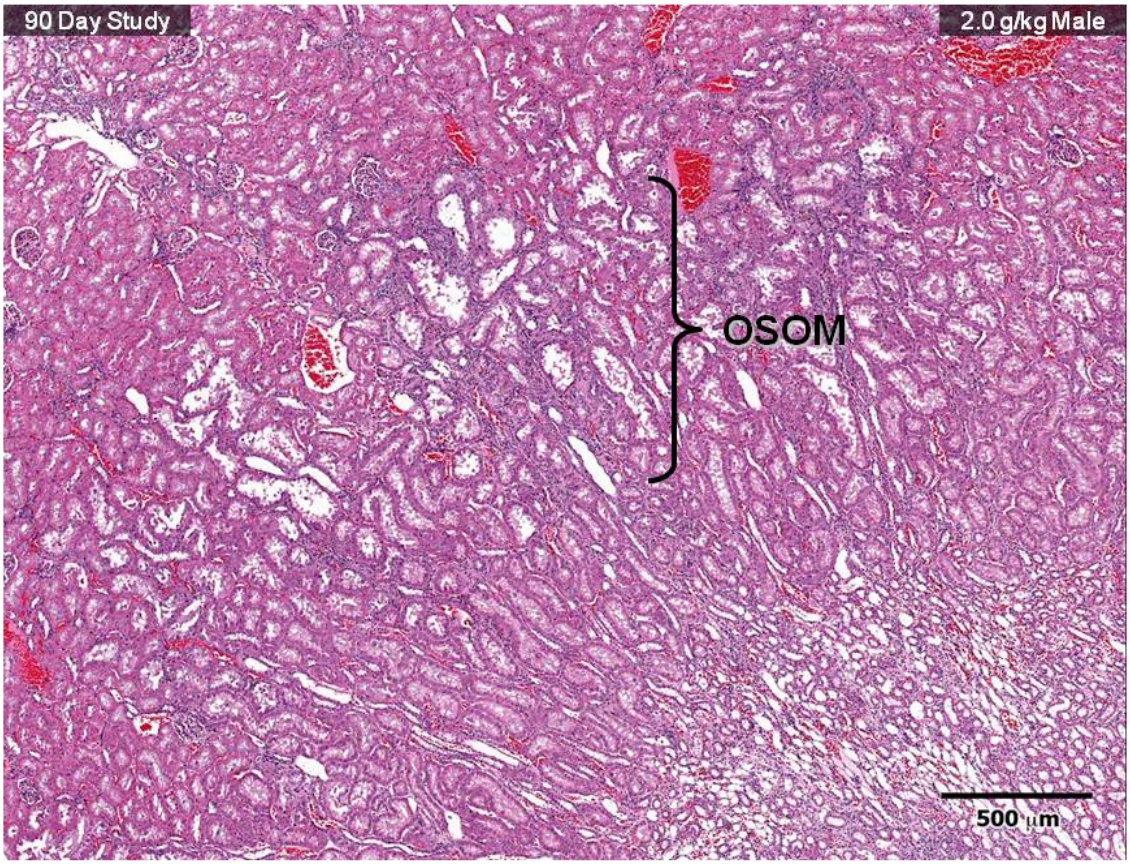
OSOM: Tubular Necrosis



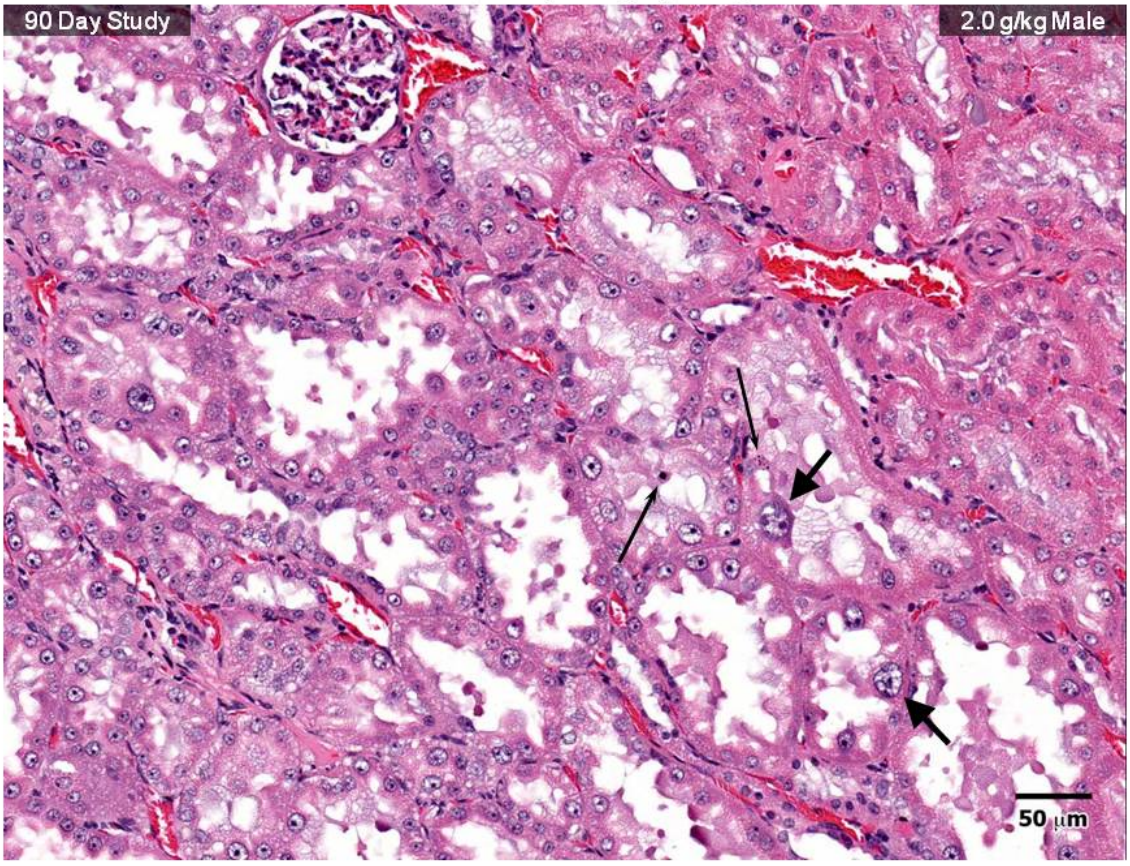
Nephrosis

- Not seen before in NTP studies
- Males > Females
- OSOM
- Severity increased with exposure duration/dose
- Lesions
  - Tubular dilation
  - Karyomegaly
  - Tubular hyperplasia
  - Tubular atrophy
  - Interstitial fibrosis
  - Collecting duct hyperplasia

OSOM: Tubule Dilation



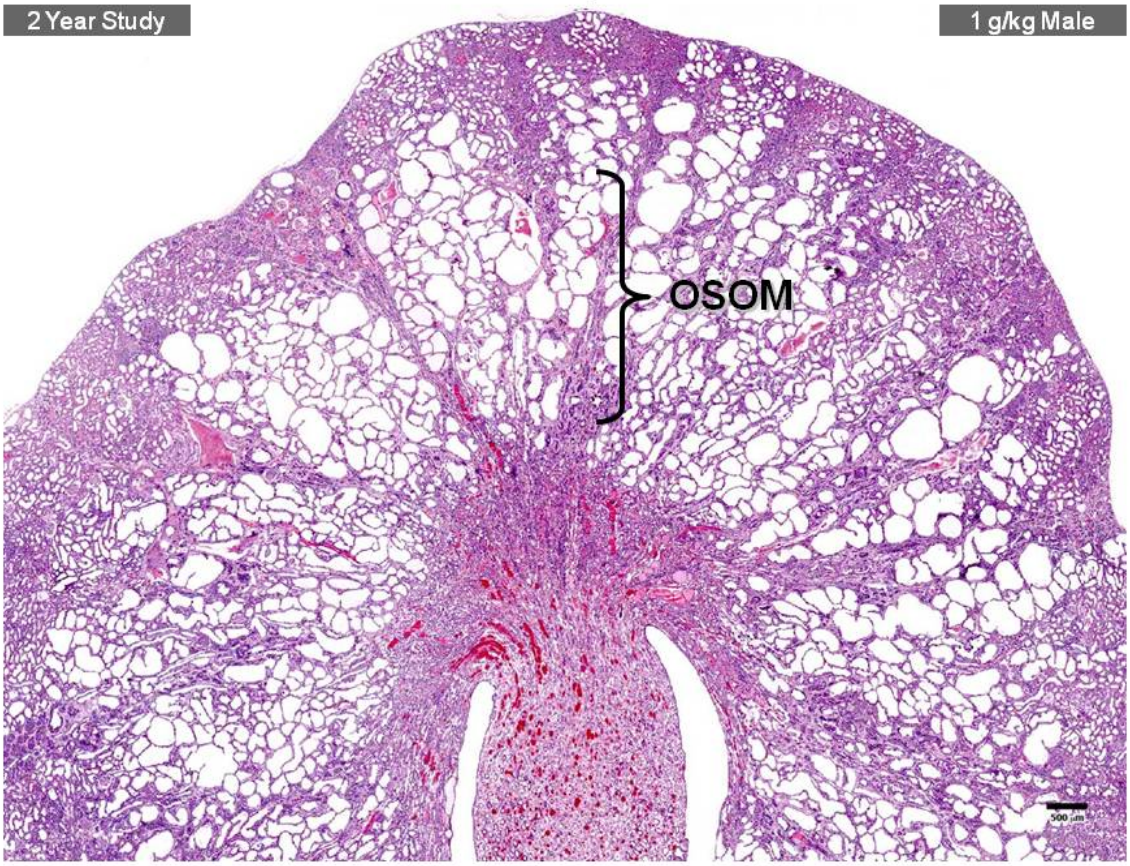
OSOM: Tubule Dilation, Karyomegaly, Single Cell Necrosis



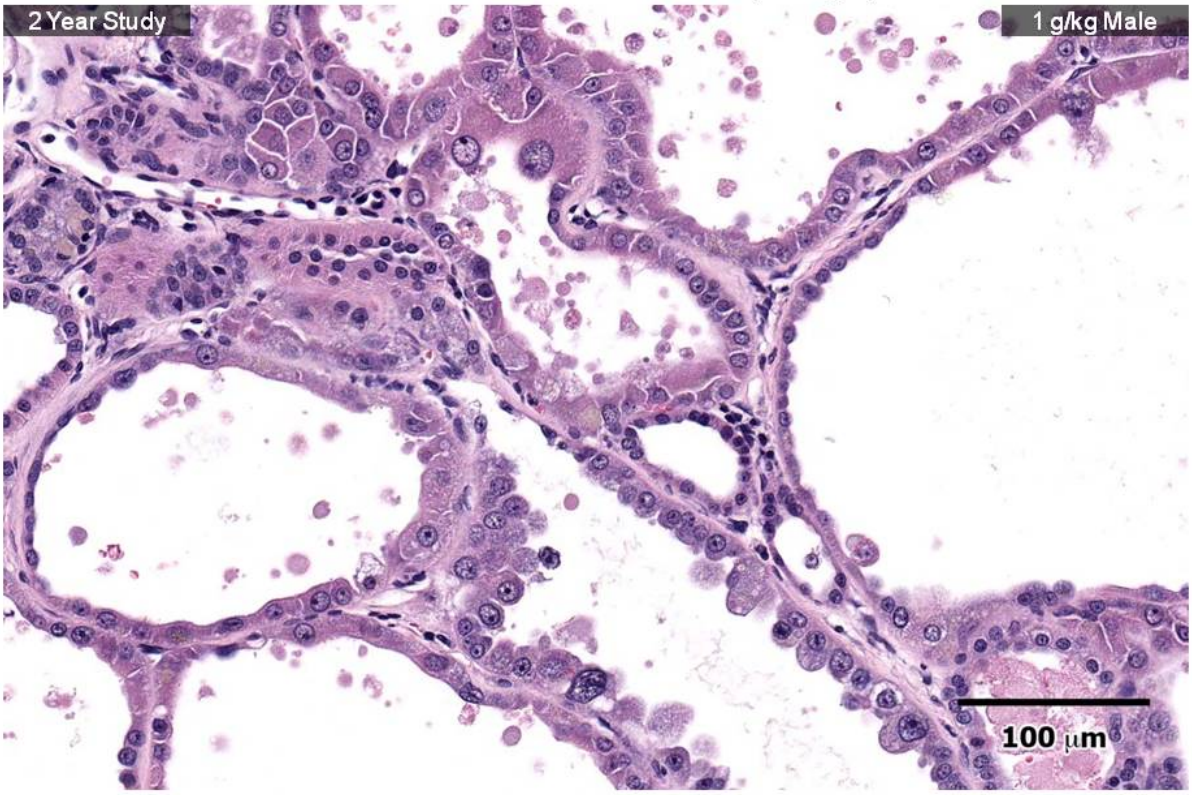
Severe Nephrosis

2 Year Study

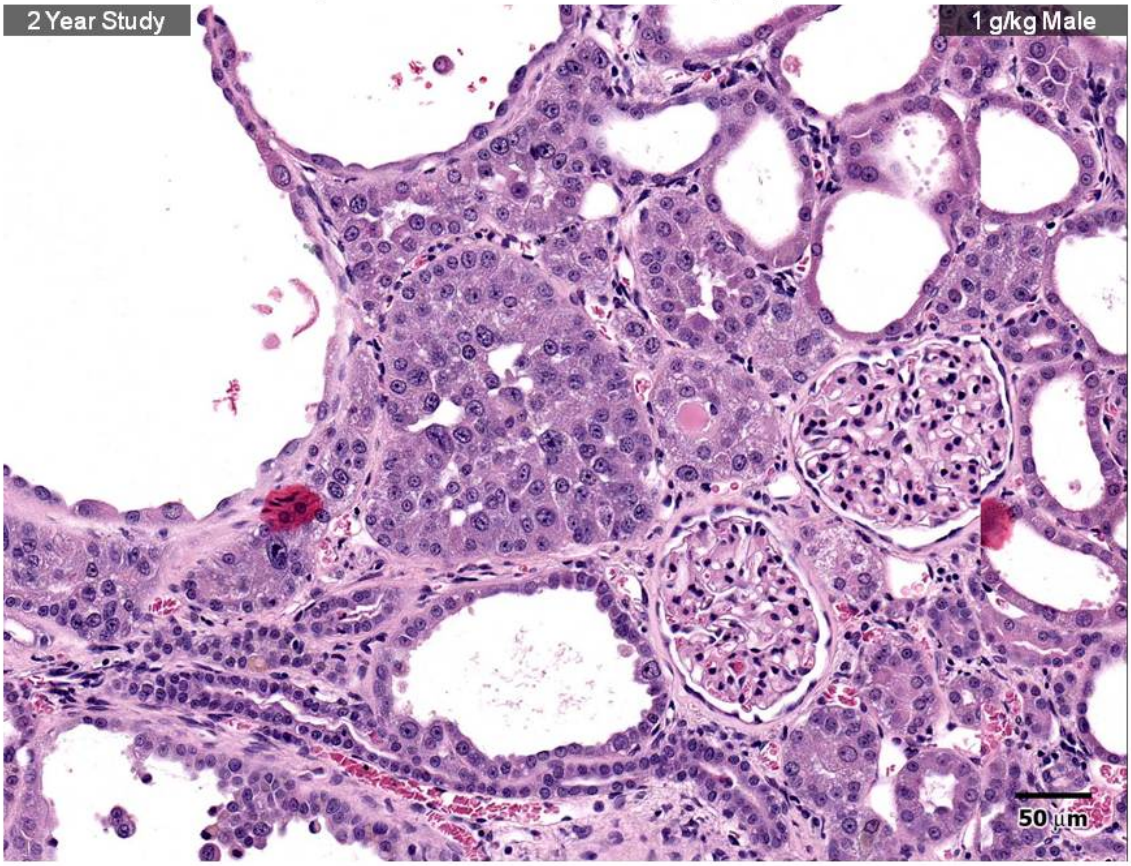
1 g/kg Male



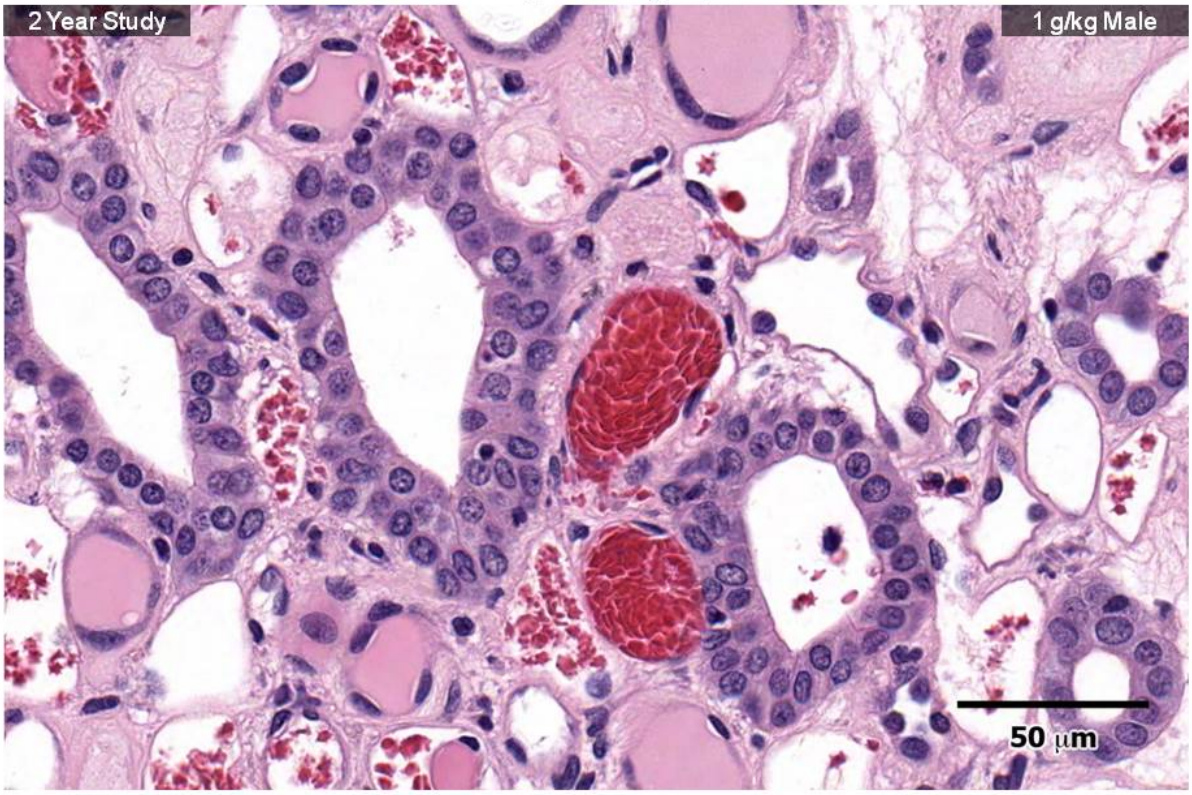
OSOM: Tubular Dilation and Karyomegaly



Nephrosis-Associated Tubule Hyperplasia



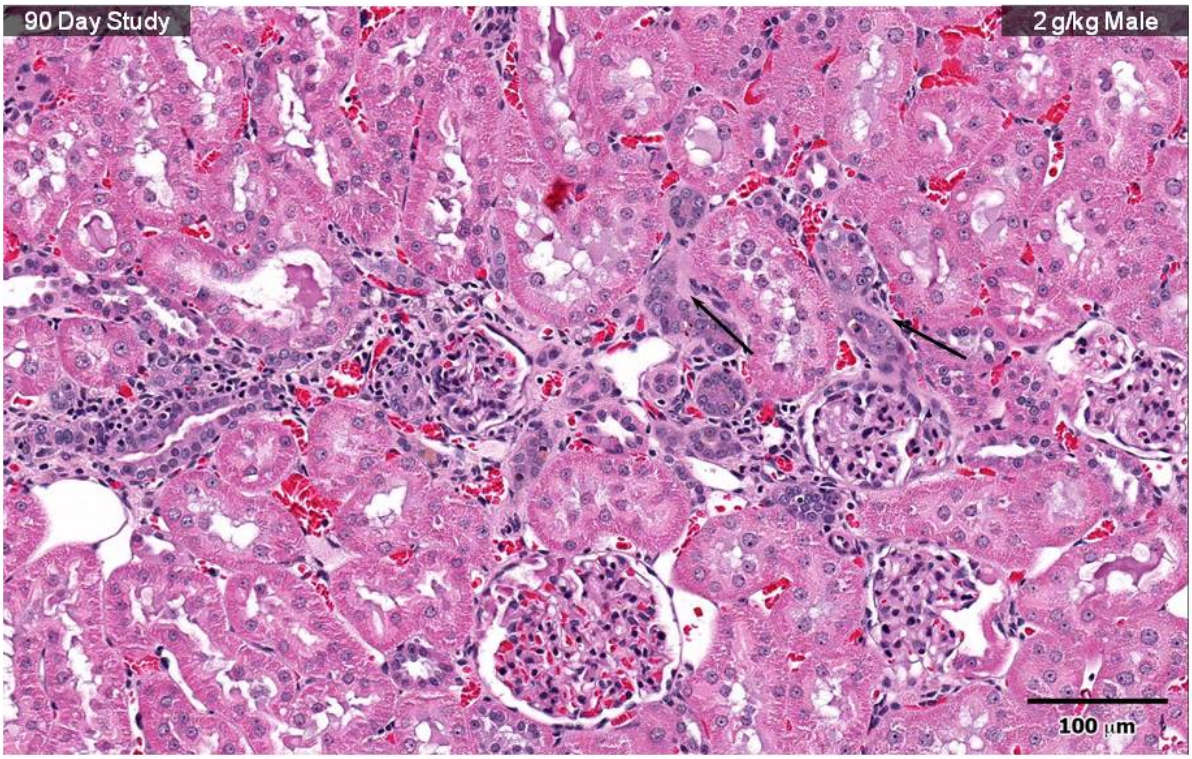
Collecting Duct Hyperplasia



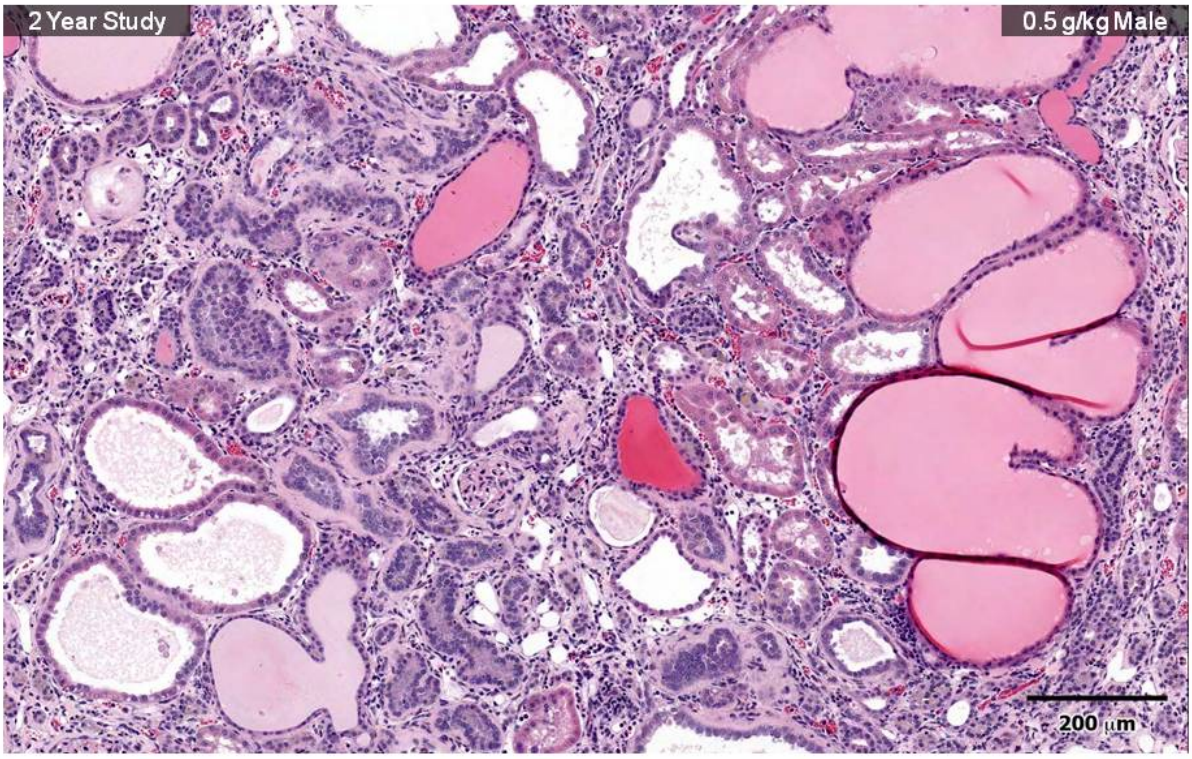
Chronic Progressive Nephropathy (CPN)

- Common spontaneous lesion - may be exacerbated by chemical exposure
- Males > Females
- Cortex
- Severity increases with age
- Lesions
  - Regenerative renal tubules (cellular basophilia, nuclear crowding)
  - Basement membrane thickening
  - Tubular hyperplasia, atrophy, dilation
  - Hyaline (protein) casts
  - Interstitial fibrosis and chronic inflammation

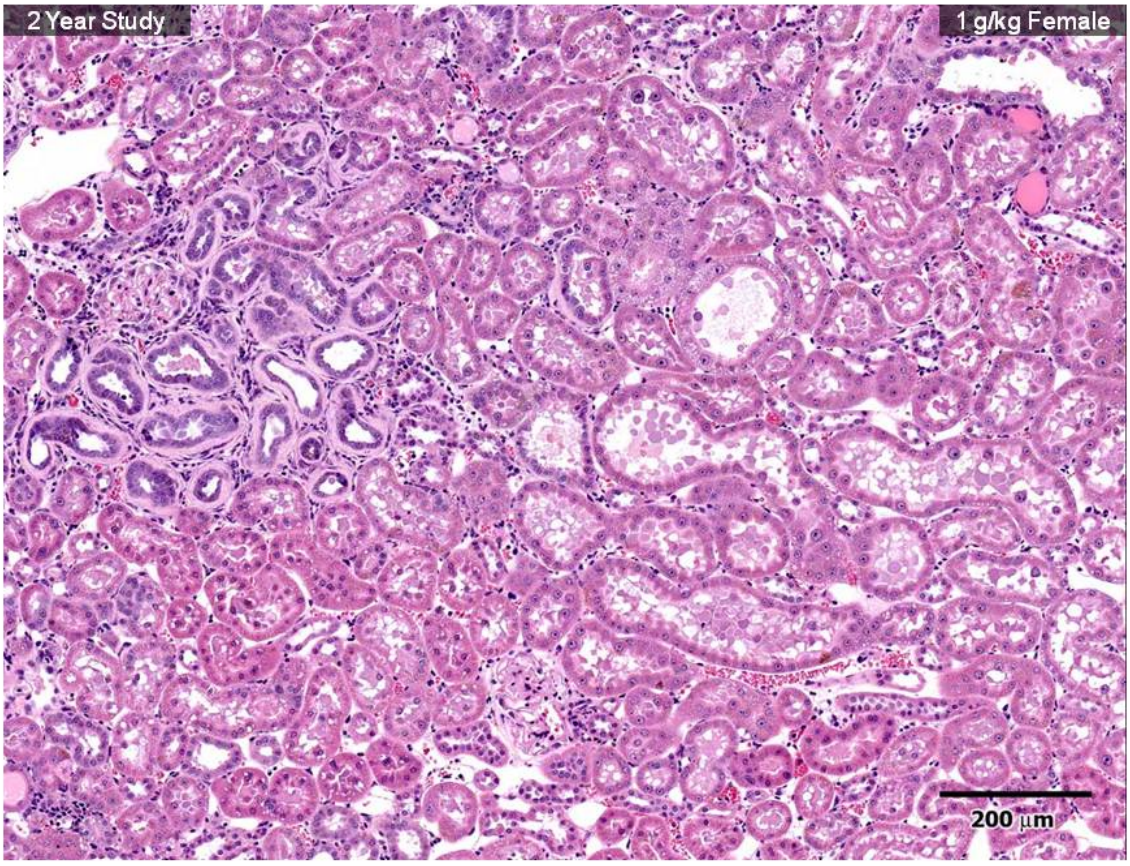
Mild CPN



Severe CPN



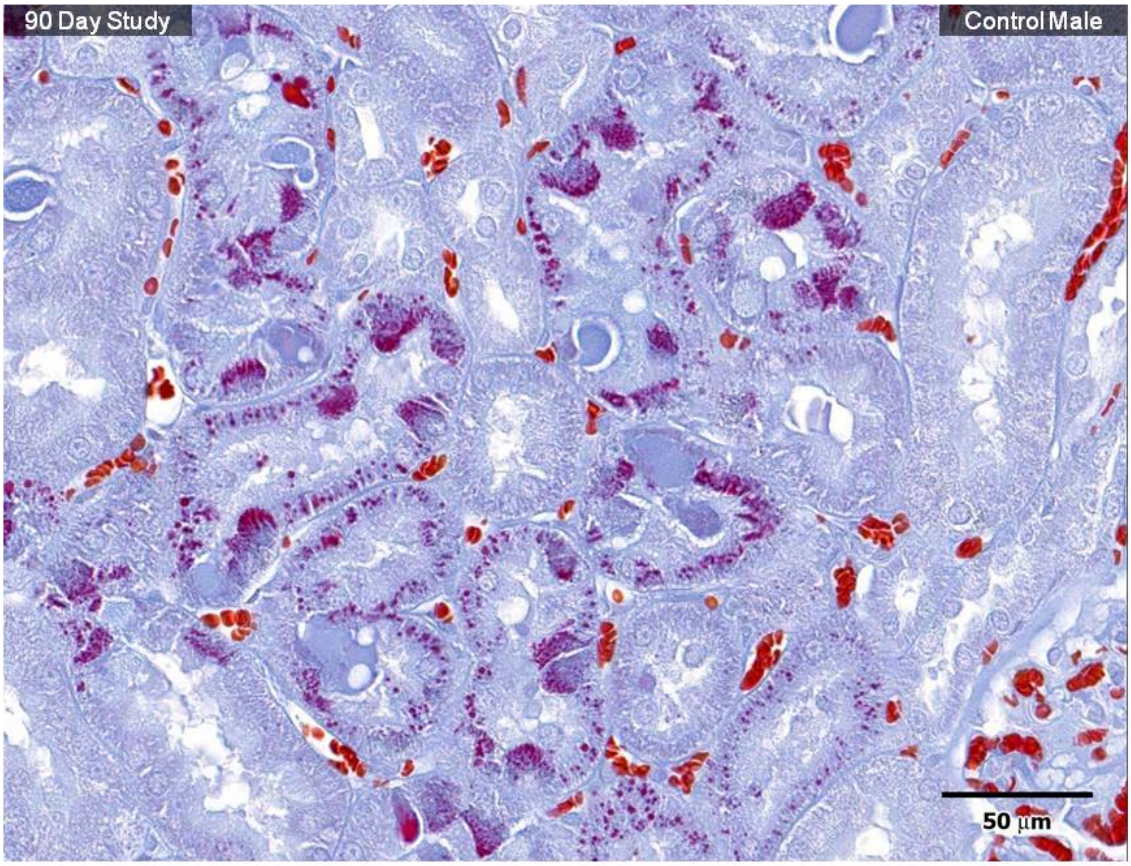
Nephrosis and CPN



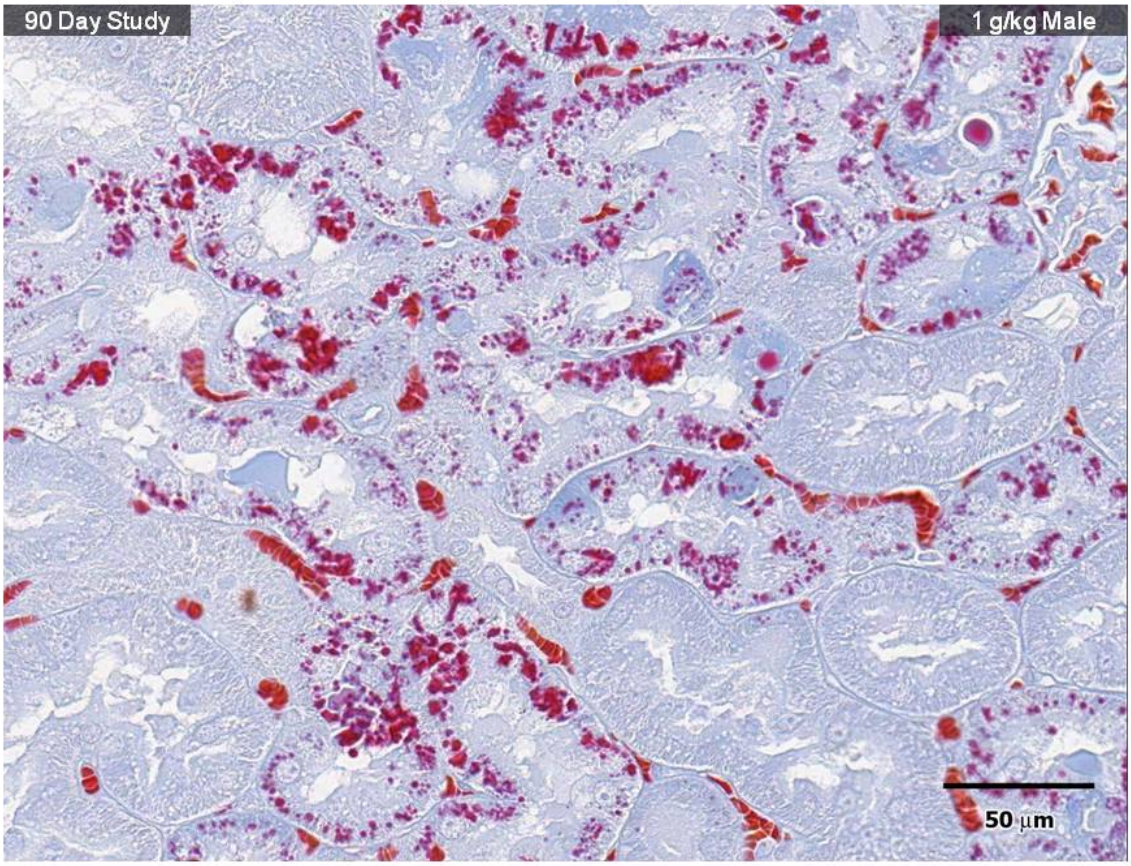
Evidence of α2u-Globulin Nephropathy

- Male rats only
- Cortex
- Severity decreases with increased exposure duration
- Lesions:
  - Hyaline droplet accumulation (90-day)
    - Change in pattern of hyaline droplets
    - Granular casts in medulla
  - Papillary mineralization - linear pattern (2-year)

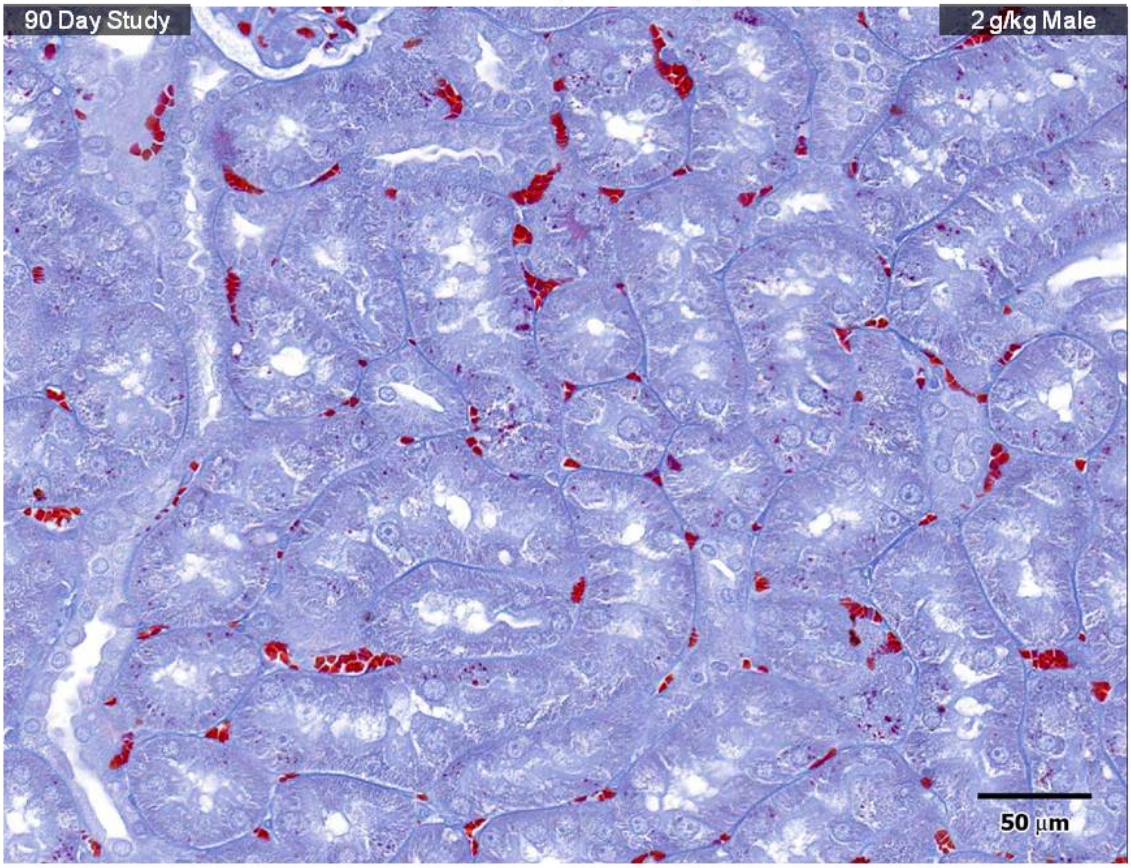
Control Hyaline Droplet Pattern



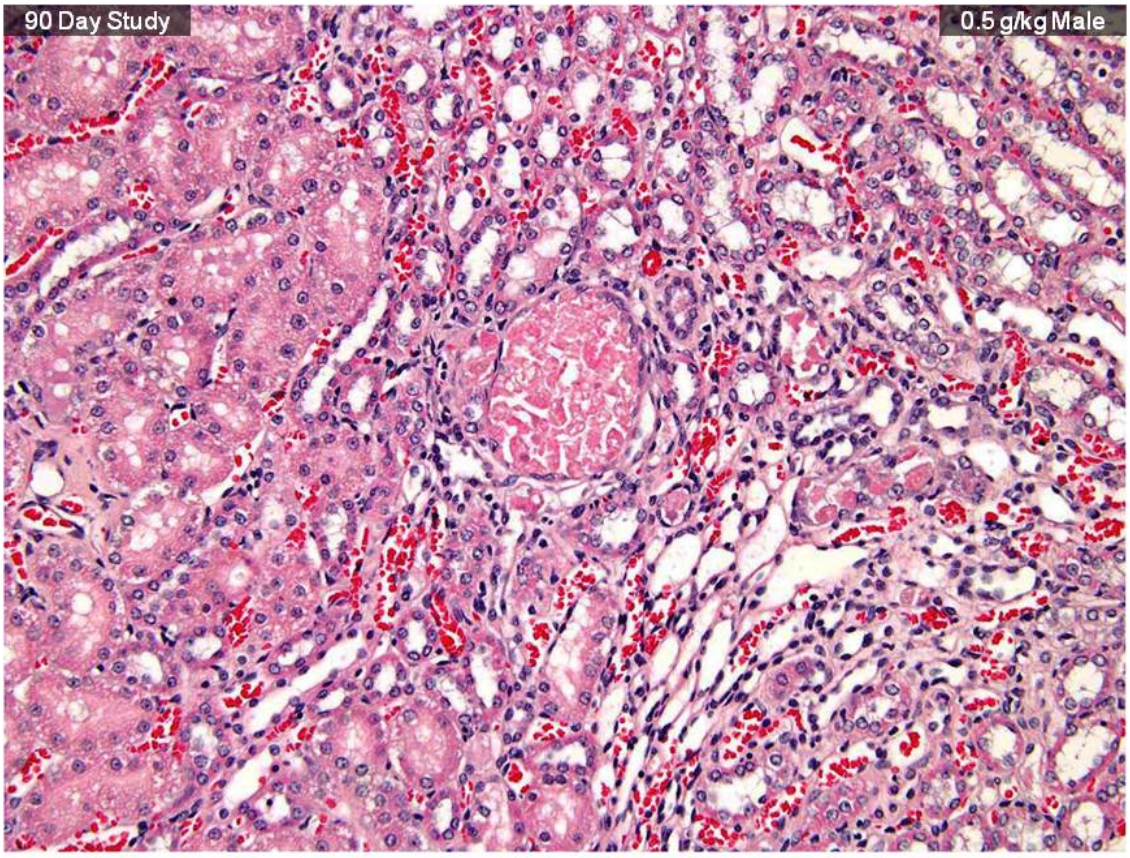
Disrupted Droplet Pattern: Crystalline Droplets, Fewer Apical Accumulations



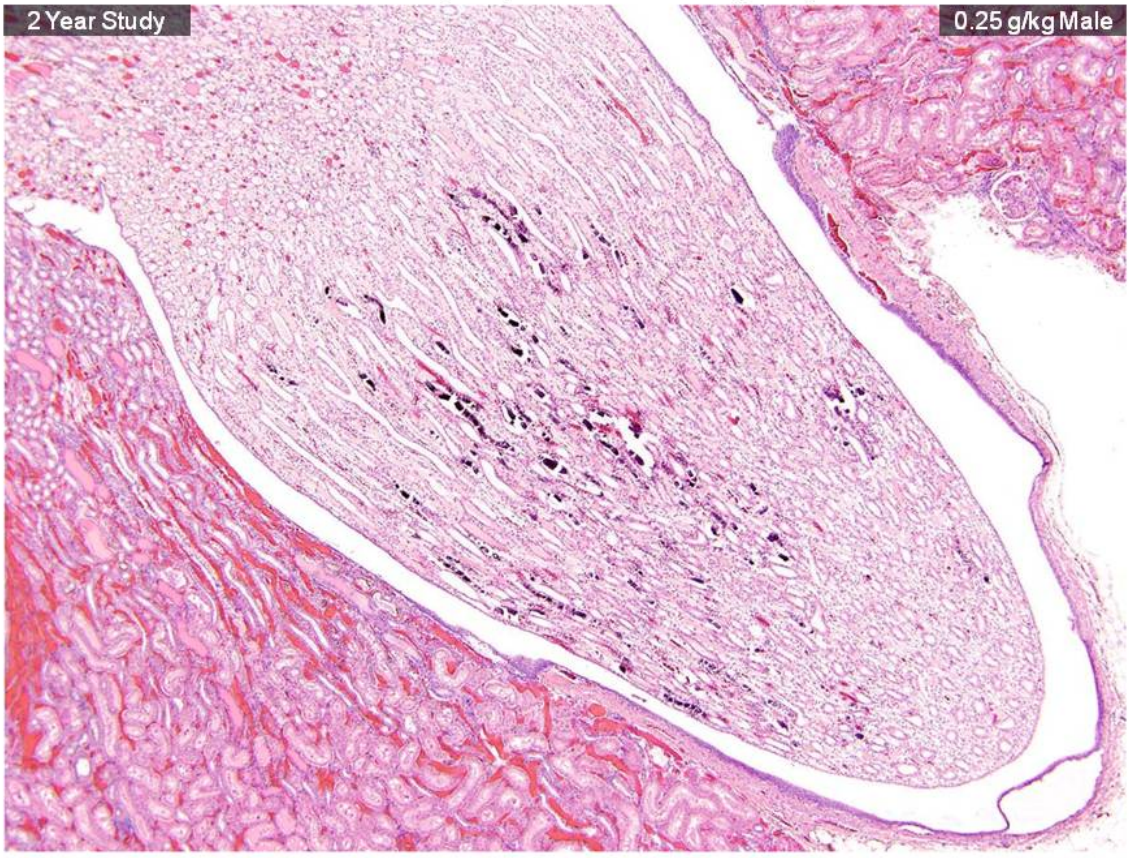
Absence of Hyaline Droplets



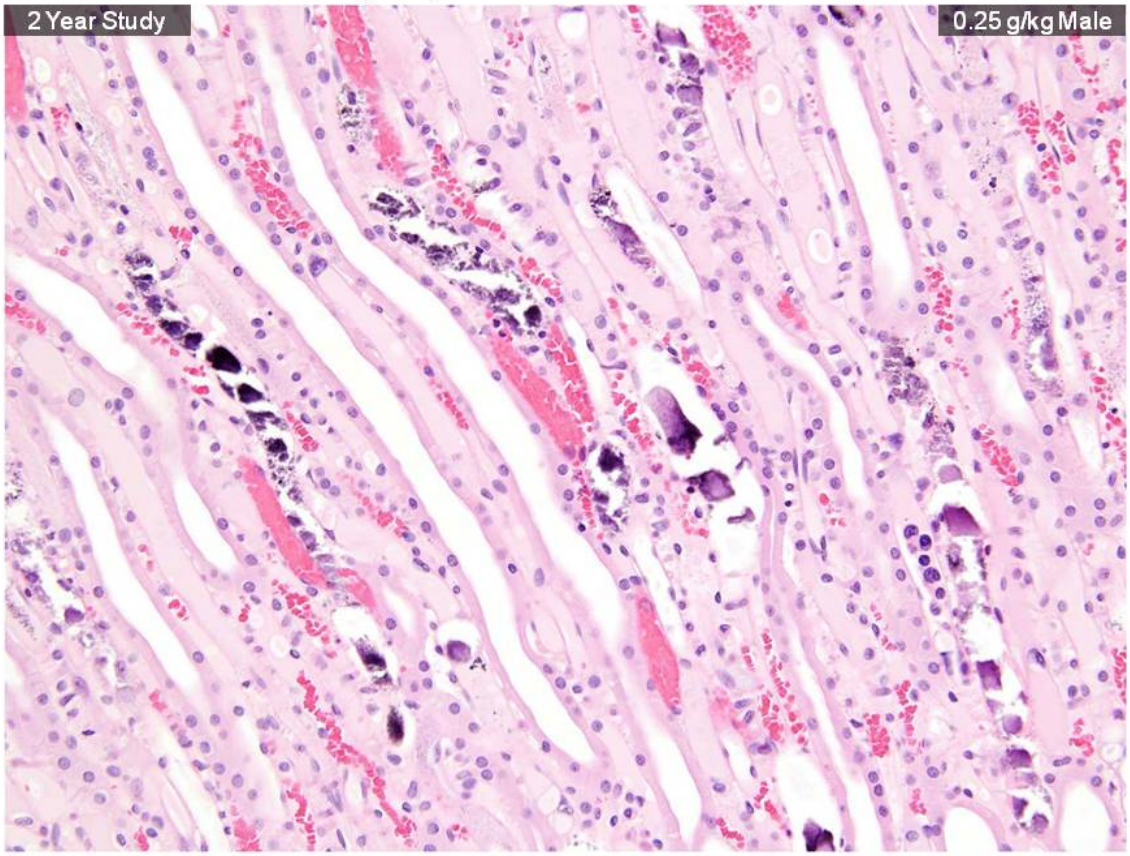
Granular Cast at OSOM/ISOM Junction



Linear Papillary Mineralization (HDA)



Linear Papillary Mineralization in Loops of Henle



Summary

- There were complex degenerative tubular lesions in this study:

  Nephrosis - not seen in previous NTP studies

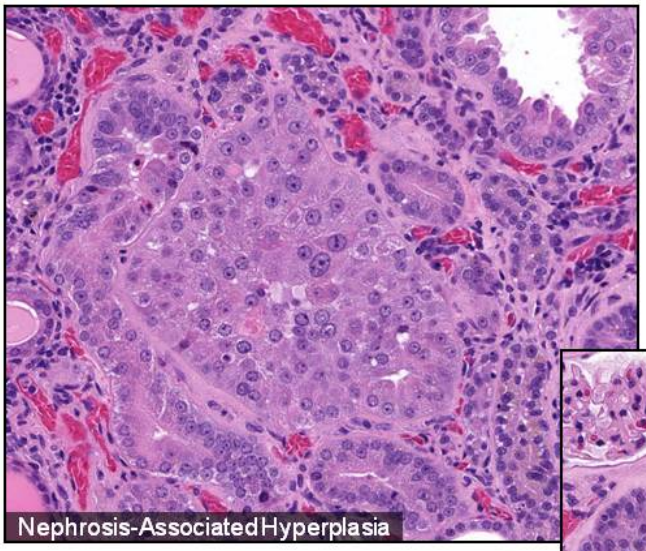
  Exacerbated CPN

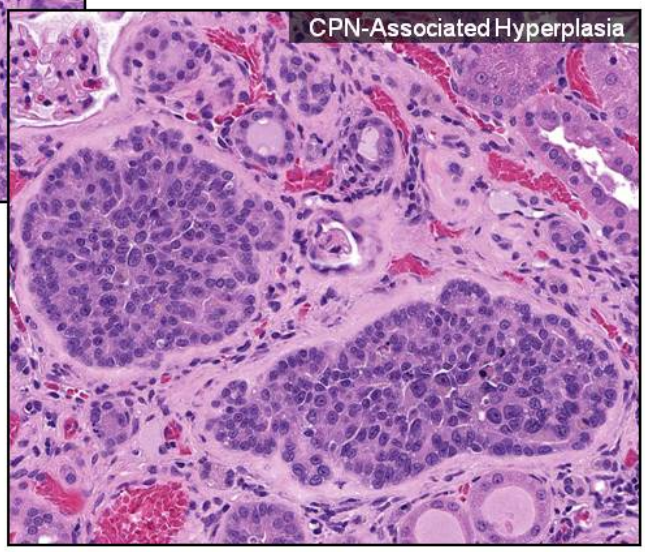
  HDA - decreased in higher doses

NTP
National Toxicology Program

HDN	CPN	Nephrosis
Hyaline Droplet Accumulation	BM Thickening	Karyomegally
Hyaline Droplet Pattern Change	Hyaline Casts	Collecting Duct Hyperplasia
Tubular Hyperplasia	Tubular Dilation	Tubular Dilation
Granular Casts	Tubular Hyperplasia	Tubular Hyperplasia
Renal Tubular Degeneration/Single Cell Necrosis	Tubular Atrophy	Tubular Atrophy
Linear Papillary Mineralization (2 Yr.)	Chronic Inflammation	Chronic Inflammation
	Interstitial Fibrosis	Interstitial Fibrosis
	Single Cell Necrosis	Single Cell Necrosis
	Glomerular Changes	Glomerular Changes?

Renal Tubule Hyperplasia


Nephrosis-Associated Hyperplasia


CPN-Associated Hyperplasia